PATENT Case SO3321-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

Nagarajan et al. | GROUP ART UNIT: 1625

SERIAL NUMBER: 09/881,913 | EXAMINER: B. Dentz

FILED: June 15, 2001 | DATE: January 24, 2003

TITLE: HETEROARYLALKANOIC ACIDS AS INTEGRIN RECEPTOR ANTAGONISTS

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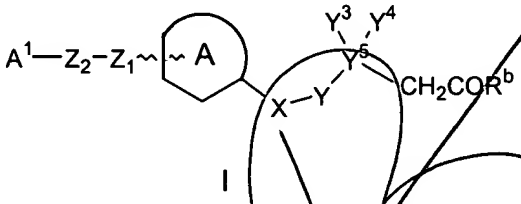
Linda Haley Date: January 24, 2003

APPENDIX A

COPY OF NEW CLAIMS 71-84

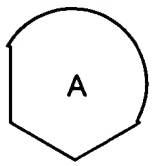
71. A compound of the Formula I

A1



I

or a pharmaceutically acceptable salt thereof, wherein



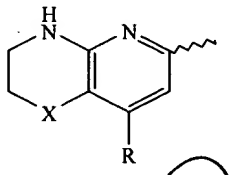
is a thiazole or isoxazole, optionally substituted with one or more substituent selected from the group consisting of alkyl, haloalkyl, aryl, heteroaryl, halogen, alkoxyalkyl, aminoalkyl,

hydroxy, nitro, alkoxy, hydroxyalkyl, thioalkyl, amino, alkylamino, arylamino, alkylsulfonamide, acyl, acylamino, alkylsulfone, sulfonamide, allyl, alkenyl, methylenedioxy, ethylenedioxy, alkynyl, carboxamide, cyano, and $-(CH_2)_mCOR$;

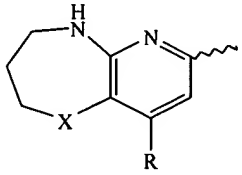
m is 0-2;

R is selected from the group consisting of hydroxy, alkoxy, alkyl, amino and sulfone;

A^1 is selected from the group consisting of

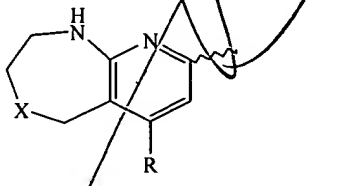


X = CH_2, O, S, SO_2, CO, CF_2, CMe_2
R = H, Me, OMe, OH, NR_2



X = CH_2, O, S, SO_2, CO, CF_2, CMe_2
R = H, Me, OMe, OH, NR_2

and



X = CH_2, O, S, SO_2, CO, CMe_2
R = H, Me, OMe, OH

; optionally substituted by one or more R^k selected from the group consisting of hydroxy, alkyl, alkoxy, alkoxyalkyl, thioalkyl, haloalkyl, cyano, amino, alkylamino, halogen, acylamino, sulfonamide and –COR;

R is hydroxy, alkoxy, alkyl or amino;

Z_1 is selected from the group consisting of CH_2, O, CH_2O, NH, CO, S, SO, CH(OH) and SO_2;

Z_2 is a 1-5 carbon linker optionally containing one or more heteroatom selected from the group consisting of O, S and N; or

Z_1 - Z_2 contains a moiety selected from the group consisting of carboxamide, sulfone, sulfonamide, alkenyl, alkynyl, and acyl; or

Z_1 - Z_2 contains a 5- or 6-membered aryl or heteroaryl ring optionally substituted with R^c, wherein the heteroaryl ring contains 1-3 heteroatoms selected from the group consisting of O, N and S;

R^c is selected from the group consisting of H, alkyl, haloalkyl, aryl, heteroaryl, halogen, alkoxyalkyl, aminoalkyl, hydroxy, alkoxy, carboxamide, and cyano;

wherein the carbon and nitrogen atoms of Z_1 - Z_2 are optionally substituted by a moiety selected from the group consisting of alkyl, alkoxy, thioalkyl, alkylsulfone, aryl, alkoxyalkyl, hydroxy, alkylamino, heteroaryl, alkenyl, alkynyl, carboxyalkyl, halogen, haloalky and acylamino;

X-Y contains a moiety selected from the group consisting of acyl, alkyl, sulfonyl, amino, ether, thioether, carboxamido, sulfonamido, aminosulfonyl and olefins; or

X is selected from the group consisting of -CHR^e-, -NR^f-, -O-, -S-, -SO_2-, and –CO-;

R^e is selected from the group consisting of H, lower alkyl, alkoxy, cycloalkyl, alkoxyalkyl, hydroxy, alkynyl, alkenyl, haloalkyl, thioalkyl and aryl; wherein when R^e is hydroxy, the hydroxy group can optionally form a lactone with the carboxylic acid function of the chain;

R^f is selected from the group consisting of H, alkyl, aryl, benzyl and haloalkyl;

Y is selected from the group consisting of $(CH_2)_p$, $-CHR^g-$, $-NR^g-$, CO and SO_2;

R^g is selected from the group consisting of H, alkyl, haloalkyl, alkoxyalkyl, alkynyl, aryl, heteroaryl, aralkyl, hydroxy, alkoxy, and carboxyalkyl;

p is 0 or 1;

Y^3 and Y^4 are independently selected from the group consisting of H, alkyl, haloalkyl, halogen, aryl, arakyl, heteroaralkyl, heteroaryl, alkenes, hydroxyalkyl, and alkyne; wherein the alkyl chain is straight or branched and optionally contains one or more moieties selected from the group consisting of N, O, and S, sulfone, sulfoamide, nitrile, carboxamide, carboalkoxy or carboxyl; wherein aryl and heteroaryl rings are monocyclic or bicylic optionally containing 1-5 heteroatoms and wherein said ring may be saturated or unsaturated, and such rings may optionally be substituted by one or more substituent R^c;

with the proviso that when Y^3 or Y^4 is H, Y^5 may be C or N, otherwise Y^5 is C; and

R^b is X_2 - R^h wherein X_2 is selected from the group consisting of O, S and NR^j wherein R^h and R^j are independently selected from the group consisting of H, alkyl, aryl, aralkyl, acyl and alkoxyalkyl.

72. A compound according to claim 71, wherein

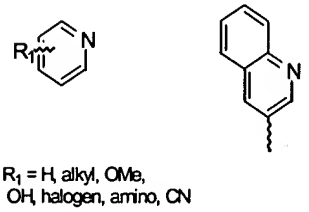
X is of $-CHR^e-$, wherein R^e is H;

Y is $-(CH_2)_p$ wherein p = 0;

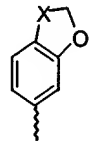
Y^5 is a carbon;

R^b is OH.

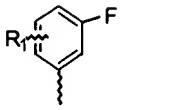
73. A compound according to Claim 72, wherein Y3 or Y4 is independently selected from the group consisting of:



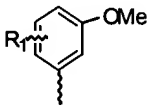
R_1 = H, alkyl, OMe, OH, halogen, amino, CN



X = CH_2, O

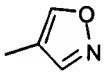


R_1 = H, alkyl, OMe, OH, halogen, amino, CN



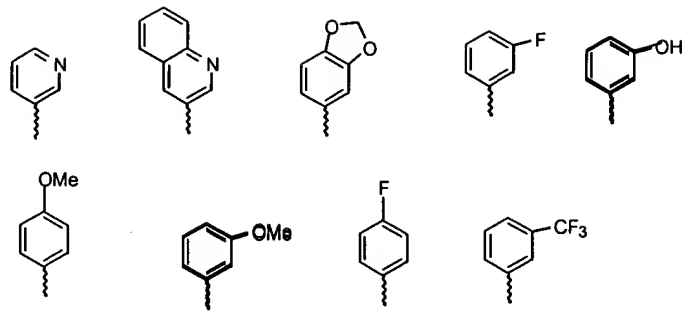
R_1 = H, alkyl, OMe, OH, halogen

X = NH, NMe, O, S



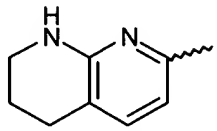
H, alkyl, CH_2B_1R (B_1 = O, SO_2, S, CO; R = alkyl, aryl), CH_2OH, and (R = alkyl, aryl, alkoxyalkyl)

74. A compound according to claim 72, wherein Y^3 or Y^4 is independently selected from the group consisting of



H, Me, Ph, Et, Pr, i-Pr, and CH_2OCH_2Ph

75. A compound according to claim 74, wherein A^1 is



76. The method according to Claim 71 wherein the compound selected from the group consisting of

(2-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-cyclopropyl)-acetic acid;

3-Phenyl-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-Pyridin-3-yl-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

3-Pyridin-3-yl-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

(2-{3-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-cyclopropyl)-acetic acid;

(2-{4-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-cyclopropyl)-acetic acid;

3-Phenyl-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-Pyridin-3-yl-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-Phenyl-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;

3-Pyridin-3-yl-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid

(2-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-cyclopropyl)-acetic acid;

3-Phenyl-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-Pyridin-3-yl-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-3-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

3-Pyridin-3-yl-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-butyric acid;

(2-{3-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-isoxazol-5-yl}-cyclopropyl)-acetic acid;

(2-{4-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-cyclopropyl)-acetic acid;

3-Phenyl-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-(2,3-Dihydro-benzofuran-6-yl)-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-(3-Fluoro-phenyl)-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-Pyridin-3-yl-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

3-Benzo[1,3]dioxol-5-yl-4-{4-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-thiazol-2-yl}-butyric acid;

Phenyl-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;
3-(2,3-Dihydro-benzofuran-6-yl)-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;
3-(3-Fluoro-phenyl)-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid;
3-Pyridin-3-yl-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid; and
3-Benzo[1,3]dioxol-5-yl-4-{3-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-isoxazol-5-yl}-butyric acid.

77. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 71 and a pharmaceutically acceptable carrier.

78. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 76 and a pharmaceutically acceptable carrier.

79. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Claim 71 and a pharmaceutically acceptable carrier/or additive and optionally a cytotoxic agent.

80. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Claim 76 and a pharmaceutically acceptable carrier/or additive and optionally a cytotoxic agent.

81. A method for treating conditions mediated by the $\alpha_v\beta_3$ integrin in a mammal in need of such treatment comprising administering an effective $\alpha_v\beta_3$ inhibiting amount of a compound of Claim 71.

82. A method for treating conditions mediated by the $\alpha_v\beta_3$ integrin in a mammal in need of such treatment compirisng administering an effective $\alpha_v\beta_3$ inhibiting amount of a compound of Claims 76.

83. The method according to Claim 81 wherein the condition treated is tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelorosis, macular degeneration, retinopathy, and arthritis.

84. The method according to Claim 82 wherein the condition treated is tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelorosis, macular degeneration, retinopathy, and arthritis.